REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the remarks herein, is respectfully requested. Claims 1-2, 7, 42, and 44 are amended, and claim 16 is canceled. The amendments are intended to further prosecution and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in a continuation of the present application. In particular, the Examiner is respectfully requested to note that an epitope peptide is defined by the specific immunological response the peptide elicts, i.e., the response is specific for a certain endogenous or exogenous antigen, and not by any particular sequence that is present in the endogenous or exogenous antigen (page 15, line 11-page 16, line 8 of the specification) (see the Amendment filed June 1, 2001). Claims 1-3, 5, 7, 13, 17-18, 31, 34-39, and 41-44 are now pending in this application.

Amended claim 1 is supported by originally-filed claim 1 and page 3, line 4 and page 17, lines 23-24 of the specification.

Amended claim 2 is supported by originally-filed claim 2 and page 3, line 4 of the specification.

Amended claim 7 is supported by originally-filed claims 2, 7 and 16 and page 3, line 4 of the specification.

Amended claim 42 is supported by originally-filed claim 1.

Amended claim 44 is supported by originally-filed claims 1 and 17.

In the Office Action dated November 25, 2002, the Examiner indicated that claims 7, 16, 38-39 and 42-44 were objected to as being dependent upon rejected claims. As those claims were only objected to, it is respectfully submitted that amended claim 7, which incorporates the language of claim 2 and claim 16, amended claim 42, which incorporates the language of claim 1, and amended claim 44, which incorporates the language of claim 1, are allowable. The Examiner is requested to consider that claim 5 was not rejected in the Office Action dated November 25, 2002, and so is presumably allowable.

The Examiner rejected claims 2, 13, 34 and 37 under 35 U.S.C. § 102(e) as being anticipated by King (U.S. Patent No. 6,106,844). The Examiner also rejected claims 1-3, 31 and 34-36 under 35 U.S.C. § 102(e) as being anticipated by Daniel et al. (Proc. Natl. Acad. Sci. USA,

93:956 (1996)). The Examiner further rejected claims 17-18 and 41 under 35 U.S.C. § 103(a) as being unpatentable over Daniel et al. These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

King discloses immunogenic peptides from vespid antigen 5 and the use of T cell epitopes of vespid antigen 5 to anergize T cell responses in sensitive individuals (abstract). Immunodominant vespid antigen 5 peptides are disclosed as useful in immunotherapy, e.g., via subcutaneous injection or intranasal administration (column 27, line 44-column 28, line 8). It is further disclosed that peptides that are antigenic in more than one mouse strain are candidates for immunodominant epitopes in antigen 5 sensitive humans (column 18, lines 51-55). However, the Examiner is requested to consider that even if a universal epitope peptide for a certain antigen in mice was identified, it is uncertain whether that the same peptide has a universal epitope for humans, as the immune response loci for mice are quite different and much less complex that the immune response loci of humans.

Peptides of antigen 5 were contacted with spleen cells from five strains of mice (Figures 4-14 and Example 1). Interestingly, although three antigen 5 peptides were recognized by 3/5 strains (60%), no peptide was recognized to a significant extent by spleen cells from all five strains of mice or even by spleen cells from 4/5 strains of mice.

King does not provide any data relating to the impact of the administration of peptides on antibody production, much less any data relating to the impact of respiratory administration of peptides on antibody production. In this regard, the Examiner is requested to consider that in Norman et al. (Am. J. Resp. Crit. Care Med., 154, 1623 (1996), of record)), the subcutaneous administration to humans of two T cell reactive peptides for allergens in cat dander (Fel1 and Fel2) resulted in a decrease in nose and lung symptoms in two groups treated with the peptides, but that none of the treated groups "showed a significant change in IgE or IgG antibody to Fel d 1" (page 1626, Table 1). Thus, T cell epitope peptide administration does not necessarily result in a decrease in aberrant, pathogenic or undesirable antibody production.

Further, prior to Applicant's disclosure, it was unclear whether antigen or peptide administration would be efficacious for an antibody-mediated disease for two reasons. First, while effective at reducing antigen-specific CD4+ responses, administration of antigen through

routes that downregulate CD4+ responses may directly stimulate B cells specific for the administered antigen (see page 2 of Applicant's specification). This stimulation may have disastrous consequences, as has been shown in marmoset EAE, where intraperitoneal administration of myelin resulted in CD4+ tolerance to myelin, but also in an acute, fatal form of EAE. The fatal form of EAE was characterized by antibody specific for the myelin oligodendrocyte glycoprotein. Second, administration of antigen through routes that stimulate Th2 cells and downregulate proinflammatory Th1 cells can stimulate antibody synthesis and cause exacerbation rather than improvement of antibody-mediated autoimmune diseases. This concern was also noted in Norman et al. with respect to the use of peptides for tolerization (i.e., peptides must be carefully selected to avoid peptides having tertiary structures recognized by IgE antibodies).

Daniel et al. disclose that insulin-dependent diabetes mellitus (IDDM) is an autoimmune disorder in which insulin-producing beta cells are specifically destroyed and that nonobese diabetic (NOD) mice, which develop IDDM, are a model for type I diabetes (page 956). It is also disclosed that while insulin autoantibodies (IAA) precede the onset of diabetes the available data indicate that T cells are the dominant mediators of beta cell destruction (page 956). Thus, IDDM is a T cell-mediated disease, not an antibody-mediated disease.

Daniel et al. also disclose that in NOD mice, the T cell response to insulin is dominated by the response to residues 9-23 of the B chain of insulin (B-(9-23)) (page 956). To further characterize the insulin response of NOD mice, Daniel et al. determined that 93% of 312 insulin-specific T cell clones obtained from 21 mice responded to B-(9-23). Such a result should not be surprising given that these mice are inbred. It was also found that administration of B-(9-23) to 4 week old female NOD mice via a single subcutaneous injection or multiple intranasal exposures reduced the percent of mice with increased blood glucose levels (Figures 3 and 4). Daniel et al. further found that intranasal administration of B-(9-23) for five consecutive days decreased the lymph node cell proliferative response (page 958).

While Daniel et al. suggest that "[i]ntranasal administration of insulin or insulin peptides may be of value for prevention of type I diabetes in human subjects" (page 960), they point out that a study reported by Keller et al. (Lancet, 341, 927 (1993), of record)), where protection was observed after subcutaneous low dose and intravenous insulin administration to subjects at risk

for IDDM, "involved relatively small group sizes and awaits confirmation" (page 960). Keller et al. measured blood levels of islet cell and insulin autoantibodies, fasting blood glucose, and first phase insulin release in these patients. Daniel et al., however, question the efficacy of insulin-based therapies as results reported by Keller et al. were obtained using human peripheral blood, which are "of questionable relevance to the disease process" (page 960).

With regard to T cell-mediated diseases, such as IDDM, it is Applicant's position that a T cell-mediated disease is different than an antibody-mediated disease. The Examiner is respectfully requested to note that a reference relating to an animal model for a T cell-mediated disease, Metzler et al. (Int. Immunol., 5, 1159 (1993)), was cited against the claims under § 103(a) in the Office Action mailed February 18, 1999. In Applicant's response, it was noted that Metzler et al. related to a specific T cell-mediated, not an antibody-mediated disease. Notably, Metzler et al. was not employed as a reference against the claims in subsequent Office Actions.

Moreover, it appears that inherency is the underlying basis for the § 102 rejections. The Examiner is respectfully requested to consider that inherency may not be established by probabilities or possibilities regarding what may have resulted in the prior art. In re Oerlich, 666 F.2d 578, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). When "relying upon the theory of inherency, the Examiner must provide basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." M.P.E.P. § 2112, *citing* Ex parte Levy, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis on original).

As discussed above neither King nor Daniel et al. supports the position that respiratory administration of peptides necessarily reduces or inhibits aberrant, pathogenic or undesirable antibody production. Accordingly, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 102.

With respect to the § 103(a) rejection, Daniel et al. provide no motivation to employ peptide therapy for an antibody-mediated disease, as Daniel et al. relate to a T cell-mediated disease. Moreover, although Daniel et al. report that nasal administration of a peptide decreased the lymph node proliferative response and blood glucose levels in mice immunized with insulin-derived peptides, the results were obtained in a model for a T cell-mediated disease which

employed inbred mice, and those result cannot be employed to predict success for an antibody-mediated disorder or for non-inbred organisms. Further, Daniel et al. fail to provide a reasonable expectation that peptide therapy for an antibody-mediated disease would be effective.

Hence, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date April 25, 2003

By _____
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Box AF, Commissioner of Patents, Washington, D.C. 20231, on this 25th day of April 2003

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Name

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